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13. SUPPLEMENTARY NOTES

14. ABSTRACT

During the Year 2 POP (08 MAR 2014 – 07 MAR 2015), a number of personnel, including Research Scientist and Research Assistant I, were hired. USUHS IRB #1 and HRPO approvals were obtained for the primary study. Cognitive efficacy tasks were tested, revised, and finalized for the primary study. EEG and eye tracking equipment was set up and integrated, and study personnel received training on data collection procedures, including EEG, eye-tracking, and virtual reality driving simulator data acquisition. Data collection for the pilot study is nearly complete and data analyses are currently under way. Based upon examination of performance and self-report data, the cognitive efficacy tasks appear to successfully discriminate between workload conditions. We have begun development of algorithms to analyze EEG data. Key milestones are behind schedule due to a late start, but we are attempting to make up this time through accelerated recruitment efforts and data collection for the primary study.

15. SUBJECT TERMS

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Introduction

The objective of this project is to validate a combined EEG and eye tracking system aimed at assessing compromised cognitive function stemming from mild traumatic brain injury (mild TBI). Research suggests that the neural injuries resulting from mild TBI do not always produce observable performance deficits. However, subjective ratings suggest that the level of effort required to perform at a given level can be higher with mild TBI; associated neuroimaging data reveal a broader recruitment of cortical neurons to accomplish tasks in mild TBI relative to uninjured individuals [1-3]. The research described here combines information from two distinct physiological sensing approaches to make inferences about injury-related changes in cognitive function using measures that are sensitive to cognitive effort. The goal is to combine the expertise of academic, military, and industry researchers to create a practical and effective neurodiagnostic assessment tool that can be used in a broad range of contexts in which cognitive assessment is relevant. Validation of the integrated EEG and eye tracking system will include evaluation of the specificity and sensitivity of these measures based on characterizations of injury severity, performance on a neurocognitive test battery, and self-report measures of cognitive efficacy. We will also include functional magnetic resonance imagining (fMRI) and diffusion tensor imaging (DTI) to characterize the extent of functional cortical recruitment and white matter injury, respectively. The inclusion of fMRI and DTI will provide an objective basis for cross-validating the EEG and eye tracking system. Both the EEG and eye tracking data will be collected in the context of a dual-task experimental paradigm with visual target detection.

Keywords

TBI, concussion, saccadic, eye tracking, EEG, cognition

Overall Project Summary

During the Year 2 period of performance (03/08/2014 – 03/07/2015), significant progress was made in the pilot study and cognitive task development. Key milestones are approximately 4 quarters behind schedule due to delays in initial contract/subaward negotiations and transition to a new laboratory location. The laboratory transition was conducted in order to mitigate the negative impact of changes to base access policies implemented at the Naval Support Activity Bethesda (NSAB), resulting in a longer, more difficult process to acquire base access for many participants. We will attempt to make up time through accelerated recruitment and data collection efforts. The Fusion primary study has been approved by USU IRB #1 and HRPO; recruitment efforts and data collection will commence in April 2015. Please note that carry-forward funds will be used to complete tasks initially scheduled for Year 2 but now scheduled for Year 3.

Progress related to specific milestones as outlined in the statement of work is outlined below:

Hire and train research personnel. Personnel, including a Research Scientist and a Research Assistant I were hired. Training for primary study procedures including neuropsychological testing, eye-tracking, virtual reality driving simulator, and EEG data acquisition is ongoing for all research personnel.

Obtain IRB approvals. USU IRB #1 approval for the primary study was received on January 12, 2015. HRPO approval for the primary study was received March 27, 2015.

Develop cognitive efficacy tasks for VR, PC, and MRI environments. Two PC-based Fusion tasks (N-back and Color Match) and one VR-based Fusion task (Coastal Route) have been developed,

tested, and revised across multiple iterations to the current final versions for the primary study. The fMRI-based Fusion task has been developed and will be tested in the near future.

The goal of the Fusion tasks is to evaluate changes in behavioral performance, saccadic performance, and brain activation that occur at each level of cognitive load. It is expected that individuals with poorer cognitive efficacy resulting from TBI will demonstrate more significant performance trade-offs and greater increases in brain activation with increasing load.

<u>Fusion N-Back Task.</u>
The Fusion N-back task is a target detection task that features three conditions requiring varying levels of cognitive workload. During the simple reaction time condition (SRT; low cognitive workload), participants must fixate on a cross in the center of the screen. After a period of time, the cross is replaced by one of three cues: directional arrow (DC), mis-directional arrow (MDC), or no cue (NC; the cross persists). After 200ms, a target (white circle) appears on the left or the right. Participants are instructed to shift their gaze to the target and press a button on the response box as quickly as possible. The choice reaction time condition (CRT; moderate cognitive workload) is similar to the SRT condition, except the targets appear on the left or right as blue or green circles. Participants must gaze at the target and press one button if the target is green and a different button if the target is blue. The 1-back condition (high cognitive workload) requires participants to remember the color of the last target that appeared (blue or green). When the next target appears, participants must gaze at the target and press a button based on the color of the previous target.

<u>Fusion Color Match Task.</u>
The Fusion Color Match task is a dual task that requires participants to perform a vigilance task and a target detection task simultaneously. Participants see a square in the center of the screen. When the task begins, the border of the square changes color and the participant must continually try to match the color of the border to the color of the inside of the square by pressing a button. While completing this task, the participant must also fixate on a cross that is overlaid on the center of the square. After a period of time, this cross is replaced by one of three cues (DC, MDC, or NC). After 200ms, a target (white circle) appears on the left or the right. Participants are instructed to temporarily shift their gaze to the target while continuing to adjust the color of the border of the square. Cognitive workload is manipulated by adjusting the rate at which the color of the border changes (slow = low cognitive workload, medium = moderate cognitive workload, fast = high cognitive workload).

<u>Fusion Coastal Drive</u>
The Fusion Coastal Drive takes place in the virtual reality driving simulator. Participants are instructed to drive along a coastal highway while performing the target detection task. Participants must fixate on a cross in the center of the screen which is replaced by one of three cues (DC, MDC, or NC). After 200ms, a target (white circle with a number, 0-9, in the center) appears on the left or the right. Participants are instructed to shift their gaze to the target and say the number in the target circle aloud to the examiner while trying to maintain lane position. Motor tracking (steering) difficulty is modulated by the speed of the vehicle.

<u>Fusion fMRI Task</u>
The fMRI-CET is a target detection task that features two conditions requiring varying levels of cognitive workload. This is an fMRI analog of the PC-based Fusion N-back task. During the choice reaction time condition (CRT), participants must fixate on a cross in the center of the screen. After a period of time, the cross is replaced by one of three cues (DC, MDC, or NC). After 200ms, a target (white circle with a ‘6’ or ‘9’ in the center) appears on the left or the right. Participants are instructed to shift their gaze to the target and press one button if the target is a ‘6’ and a different button if the target is a ‘9.’ The 1-back condition requires participants to remember the number of the last target that

appeared (‘6’ or ‘9’). When the next target appears, participants must gaze at the target and press one button if the number of the current target is the same as the previous target and a different button if the number of the current target is different than the previous target.

Pilot test each of the cognitive efficacy tasks among 30 healthy control participants. Data collection for the pilot study is almost completed (n = 29 of 30). Preliminary analyses of performance and self-report data suggest that the cognitive efficacy tasks successfully discriminate between workload conditions and cue types.

For the Fusion N-Back Task, Graph 1 illustrates significant main effects of load ($F(2, 30) = 8.51$, $p < .05$, partial eta squared = .362) and cue type ($F(2, 30) = 19.98$, $p < .05$, partial eta squared = .571) on saccadic reaction time. Graph 2 illustrates significant main effect of load ($F(2, 28) = 21.98$, $p < .05$, partial eta squared = .611) and cue type ($F(2, 28) = 17.412$, $p < .05$, partial eta squared = .554) on manual reaction time.

For the Fusion Color Match Task, Graph 3 illustrates significant main effects of load ($F(2, 32) = 19.236$, $p < .05$, partial eta squared = .546) and cue type ($F(2, 32) = 22.807$, $p < .05$, partial eta squared = .588) on saccadic reaction time. Graph 4 illustrates a significant main effect of load ($F(2, 46) = 17.269$, $p < .05$, partial eta squared = .429) on performance (average difference between RGB value of outer square versus the inner square).

For the Fusion Coastal Drive Task, Graph 5 illustrates a significant main effect of cue type ($F(2,8) = 7.503$, $p < .05$, partial eta squared = .652) on saccadic reaction time. Graphs 6 and 7 illustrate a significant main effect of load on average lane position ($F(2,20) = 68.559$, $p < .05$, partial eta squared = .873) and average swerving ($F(2,20) = 221.901$, $p < .05$, partial eta squared = .957).

Preliminary ERP analyses were completed for the Fusion Color Match Task and indicate that there appears to be an effect of condition and cue type in neural responses. Graphs 8 and 9 illustrate significant main effects of condition ($F(2,34) = 3.800$, $p < .05$) and cue type ($F(2,34) = 11.78$, $p < .05$) on frontal-central activation 250 – 350ms post target onset. Graphs 10 and 11 illustrate a significant main effect of cue type ($F(2,34) = 12.967$, $p < .05$) on central parietal activation 90 – 175ms post target onset. There is a trend for a main effect of condition on occipital activation 100 – 150ms post cue onset (see Graphs 12 and 13). Additional ERP analyses will be completed following refinements to the analysis pipeline.

Disseminate project plans and progress.

See *Publications, Abstracts, and Presentations* below for information about progress in disseminating project plans and progress.

Update DOD/TATRC representatives on progress at annual meeting. Dr. Ettenhofer attended the Military Operational Medicine Research Program (MOMRP) meeting at Fort Detrick, MD from July 21 – July 22, 2014. Progress updates were provided to DOD/TATRC representatives and revisions to the protocol were implemented based upon feedback received at this meeting.

Key Research Accomplishments

- Developed a novel task and methods to effectively discriminate cognitive workload using eye movements and EEG
- Algorithms are in development for integrated EEG and eye tracking analyses

Conclusions

The primary goal of the Fusion project is to develop and validate methods for evaluating changes in behavioral performance, saccadic performance, and brain activation that occur at different levels of cognitive load. It is expected that individuals with poorer cognitive efficacy resulting from TBI will demonstrate more significant performance trade-offs and greater increases in brain activation with increasing load. Preliminary analyses suggest that the Fusion tasks that will be used for integrated eye tracking and neural monitoring are able to successfully discriminate cognitive workload across difficulty levels. This provides a promising basis for the extraction of valuable data relevant to detecting cognitive efficacy after TBI. Ongoing research will evaluate the Fusion tasks for this purpose, and examine potential mechanism of any effects observed.

Publications, Abstracts, and Presentations

The following paper, describing study progress and plans, has been peer-reviewed and accepted during the project period:

Safford, A., Kegel, J., Hershaw, J., Girard, D., & Ettenhofer, M.L. (2015, Aug). *Eye-movement Based Detection of Subtle Cognitive Impairment for Enhanced Assessment of Mild Traumatic Brain Injury.* Paper to be presented at the 17th Annual Conference on Human-Computer Interaction, Los Angeles, CA. Conference proceedings published in *Lecture Notes in Computer Science*.

The following invited presentations, given by Dr. Ettenhofer during the project period, have included dissemination of scientific methods and results of this study:

Ettenhofer, M.L. (March, 2015). “Novel Technologies for Assessment and Rehabilitation of Traumatic Brain Injury.” Brain Injury Awareness Seminar, Walter Reed National Military Medical Center.

Ettenhofer, M.L. (January, 2015). “Novel Technologies for Assessment and Rehabilitation of Traumatic Brain Injury.” Annual Council of Directors Meeting, Henry M. Jackson Foundation for the Advancement of Military Medicine.

Ettenhofer, M.L. (September, 2014). “The Eyes as Windows to the Brain: A Saccadic Approach to Neuropsychological Assessment.” Neuro-Infectious Disease Seminar Series, National Institute of Neurological Diseases and Stroke, National Institutes of Health.

Ettenhofer, M.L. (June, 2014). “Eliciting and Measuring Neurocognitive Processes Using Eye Movements.” Clinical Center, National Institutes of Health, Bethesda, M.D.

Ettenhofer, M.L. (April, 2014). “Neurocognitive Eye Tracking: Rationale, Methods, and Applications.” War Related Injury and Illness Study Center (WRIISC), Veterans Affairs Medical Center, Washington, DC.

Inventions, Patents, and Licenses

None to report.

Reportable Outcomes

Nothing to report.

Other Achievements

Nothing to report.

References

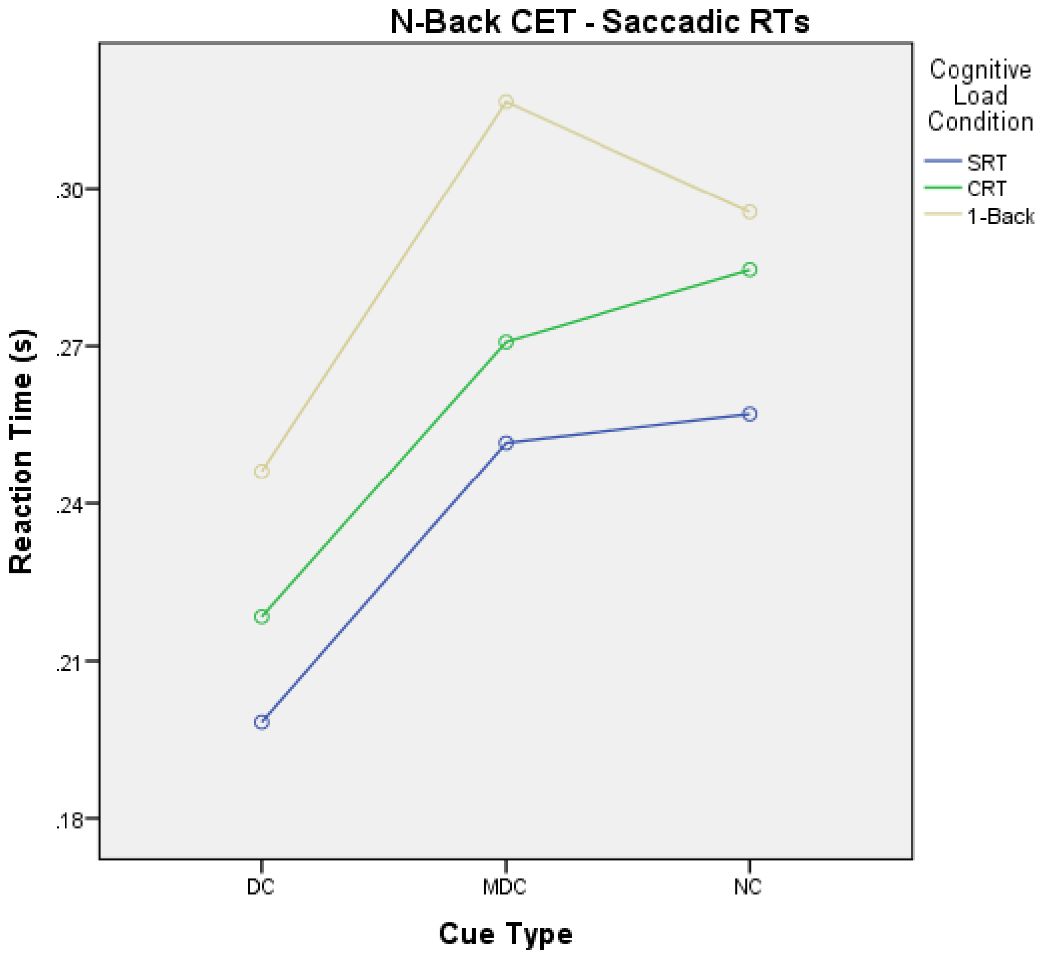
1. McAllister, T.W., et al., *Differential working memory load effects after mild traumatic brain injury*. Neuroimage, 2001. **14**(5): p. 1004-12.
2. Chen, J.K., et al., *Functional abnormalities in symptomatic concussed athletes: an fMRI study*. Neuroimage, 2004. **22**(1): p. 68-82.
3. McAllister, T., et al., *Brain activation during working memory 1 month after mild traumatic brain injury: a functional MRI study*. Neurology, 1999. **53**(6): p. 1300-8.

Appendices

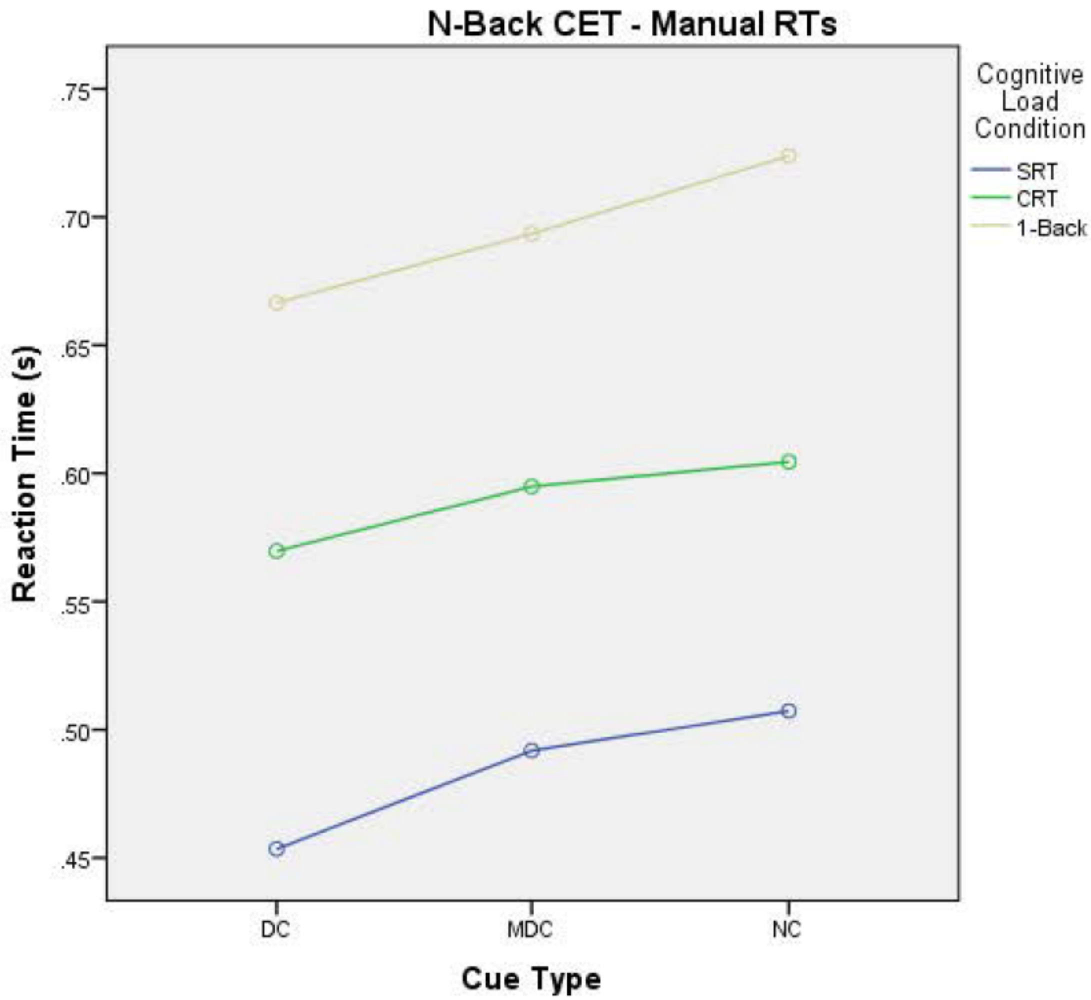
There are no appendices for this report.

Supporting Data

Graph 1

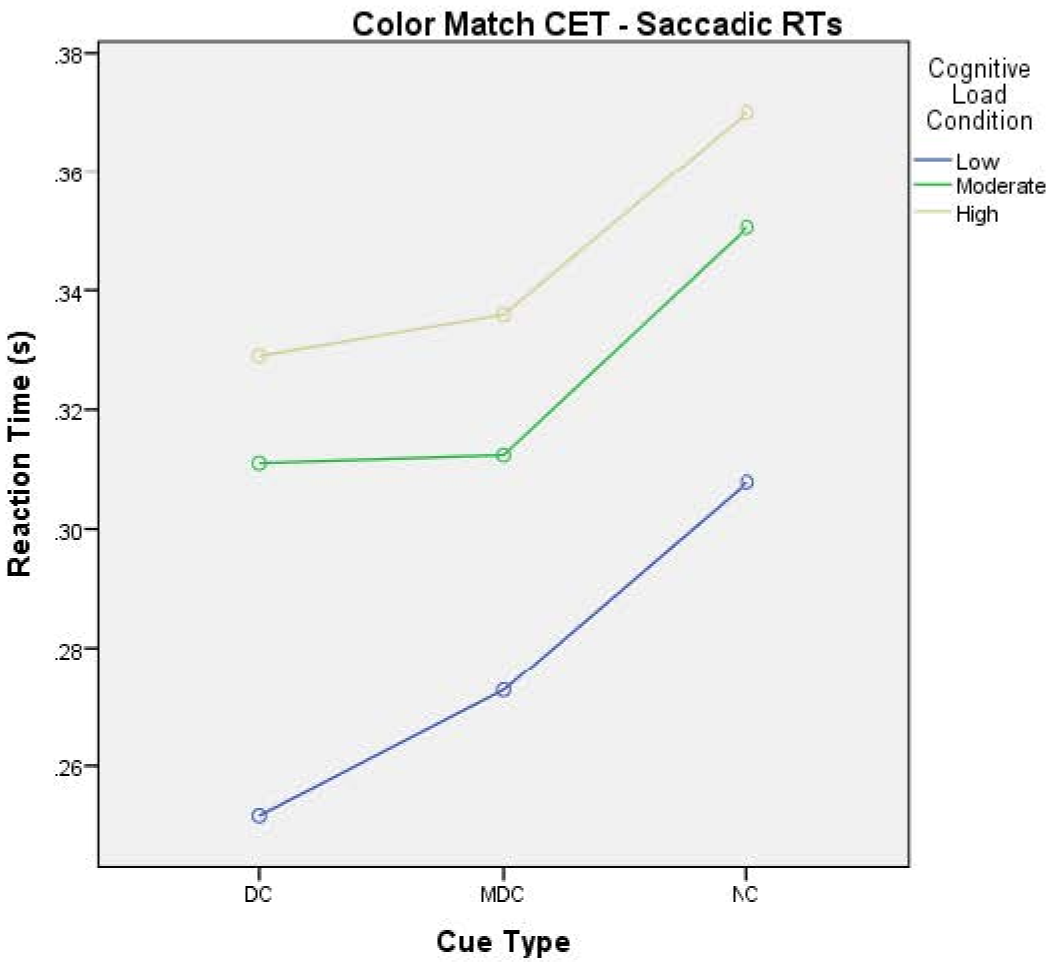


Graph 2

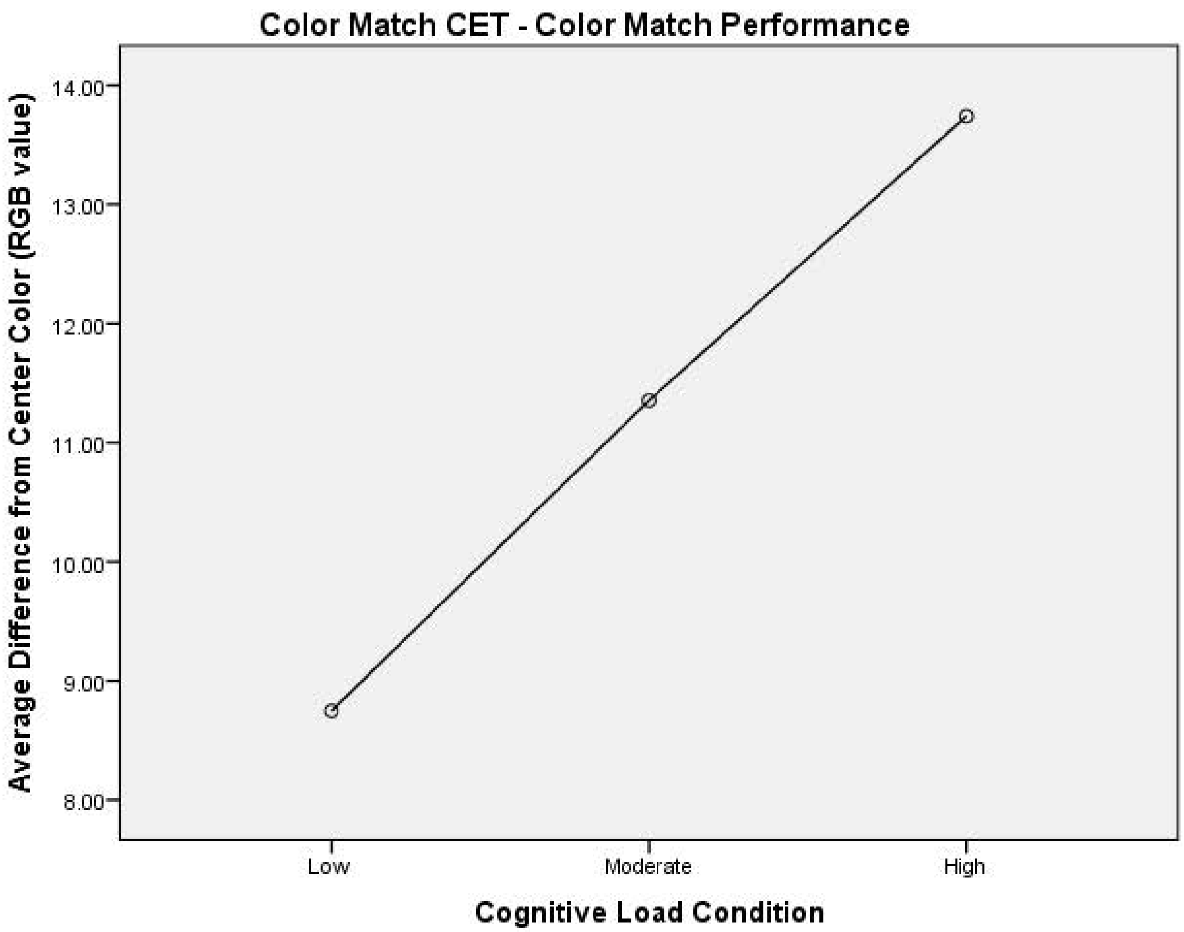


N-Back CET - Manual RTs
Reaction Time (s)
.75
.70
.65
.60
.55
.50
.45
DC
MDC
NC
Cue Type
Cognitive Load Condition
SRT
CRT
1-Back

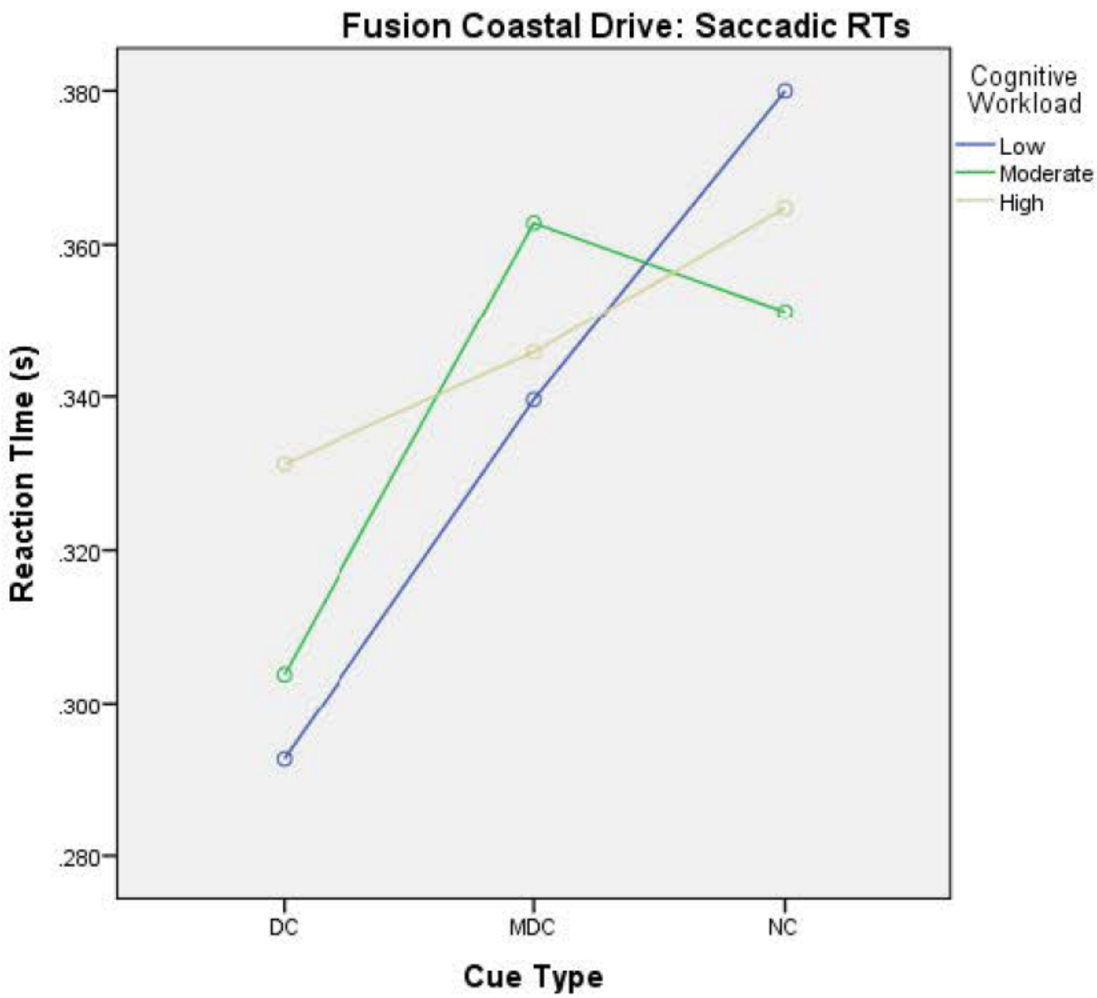
Graph 3


Color Match CET - Saccadic RTs
Reaction Time (s)
.38
.36
.34
.32
.30
.28
.26
DC
MDC
NC
Cue Type
Cognitive Load Condition
Low
Moderate
High

Graph 4

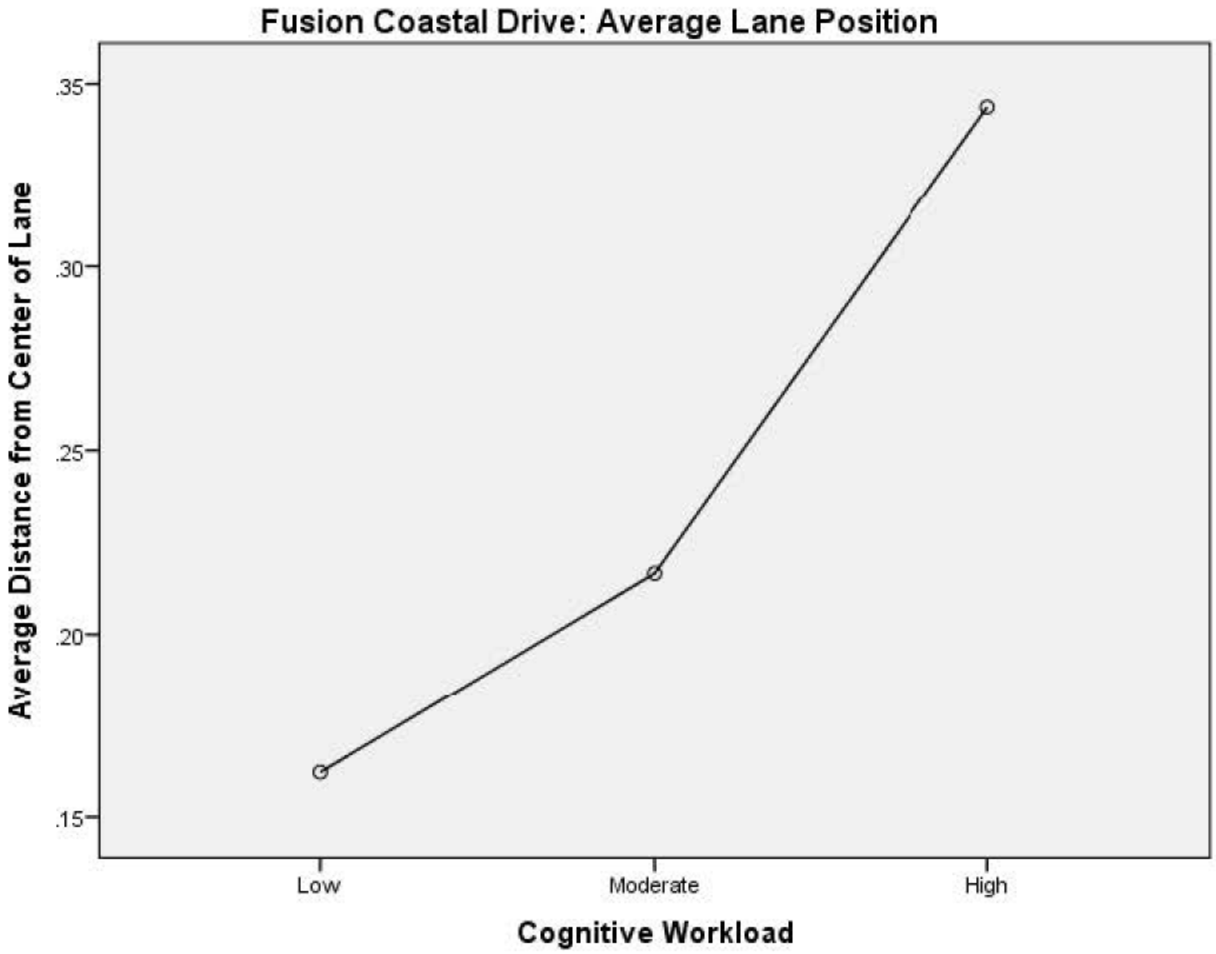

Color Match CET - Color Match Performance
Average Difference from Center Color (RGB value)
14.00
13.00
12.00
11.00
10.00
9.00
8.00
Low
Moderate
High
Cognitive Load Condition

Graph 5

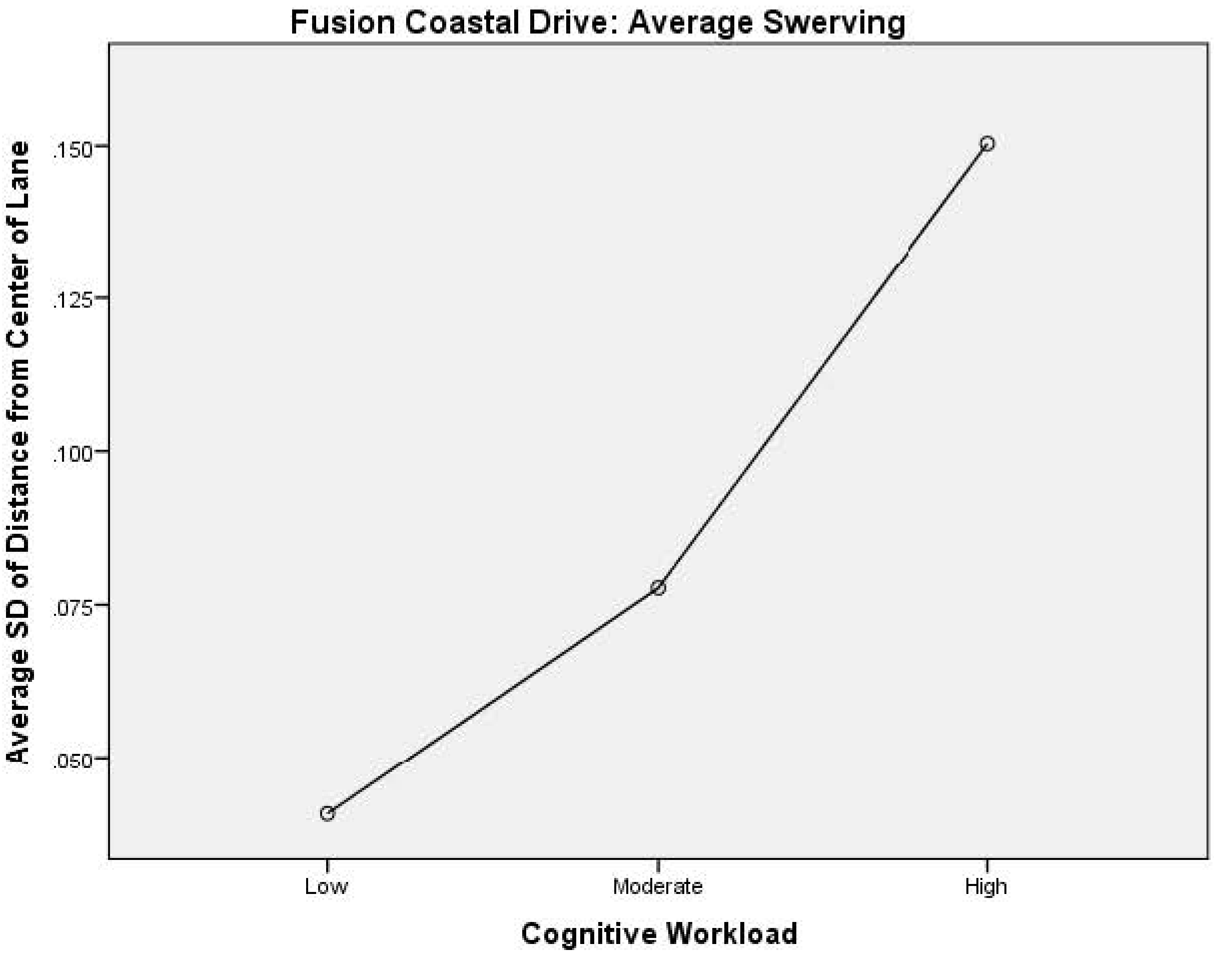


Fusion Coastal Drive: Saccadic RTs
Reaction Time (s)
.380
.360
.340
.320
.300
.280
DC
MDC
NC
Cue Type
Cognitive Workload
Low
Moderate
High

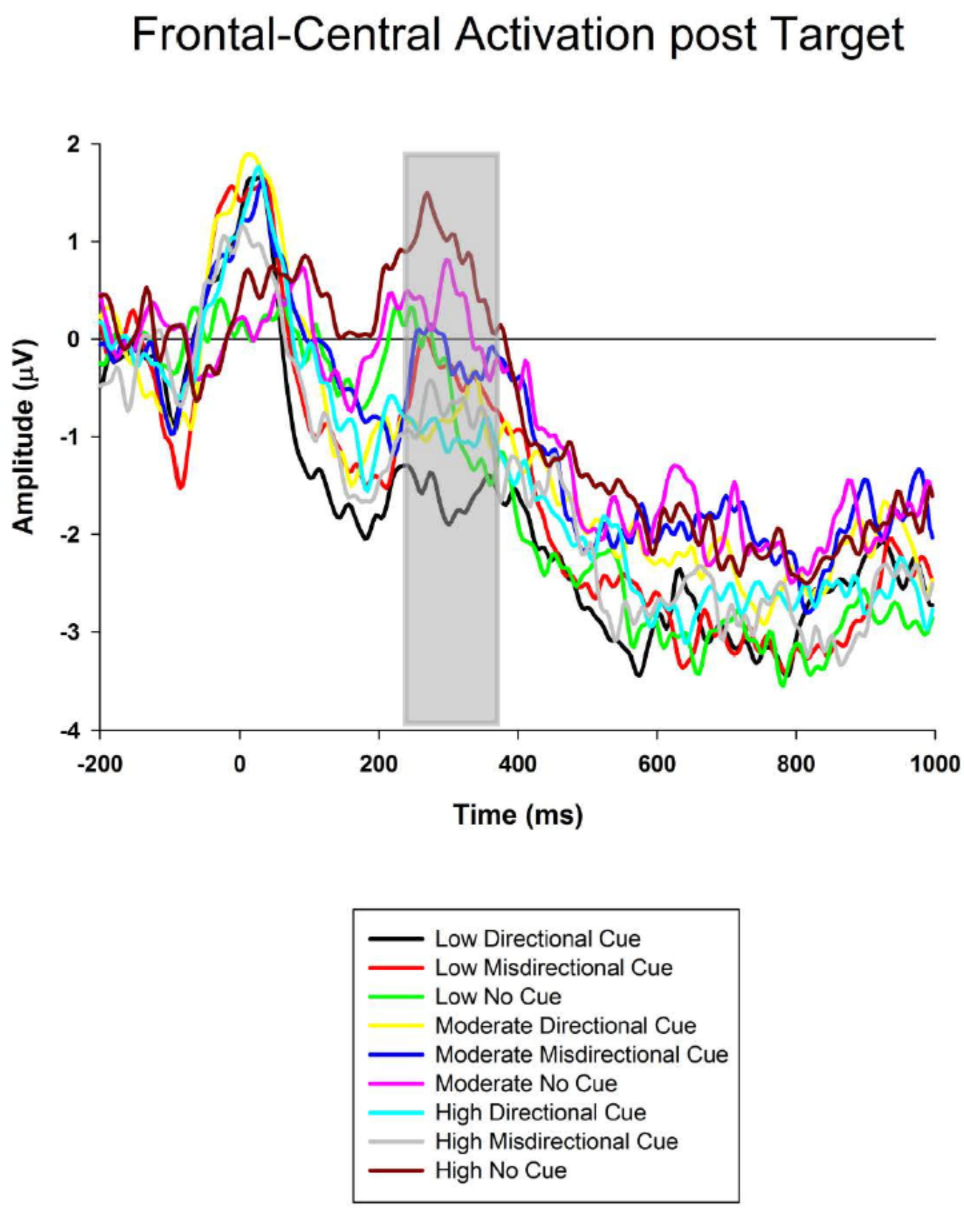
Graph 6


Fusion Coastal Drive: Average Lane Position
Average Distance from Center of Lane
.35
.30
.25
.20
.15
Low
Moderate
High
Cognitive Workload

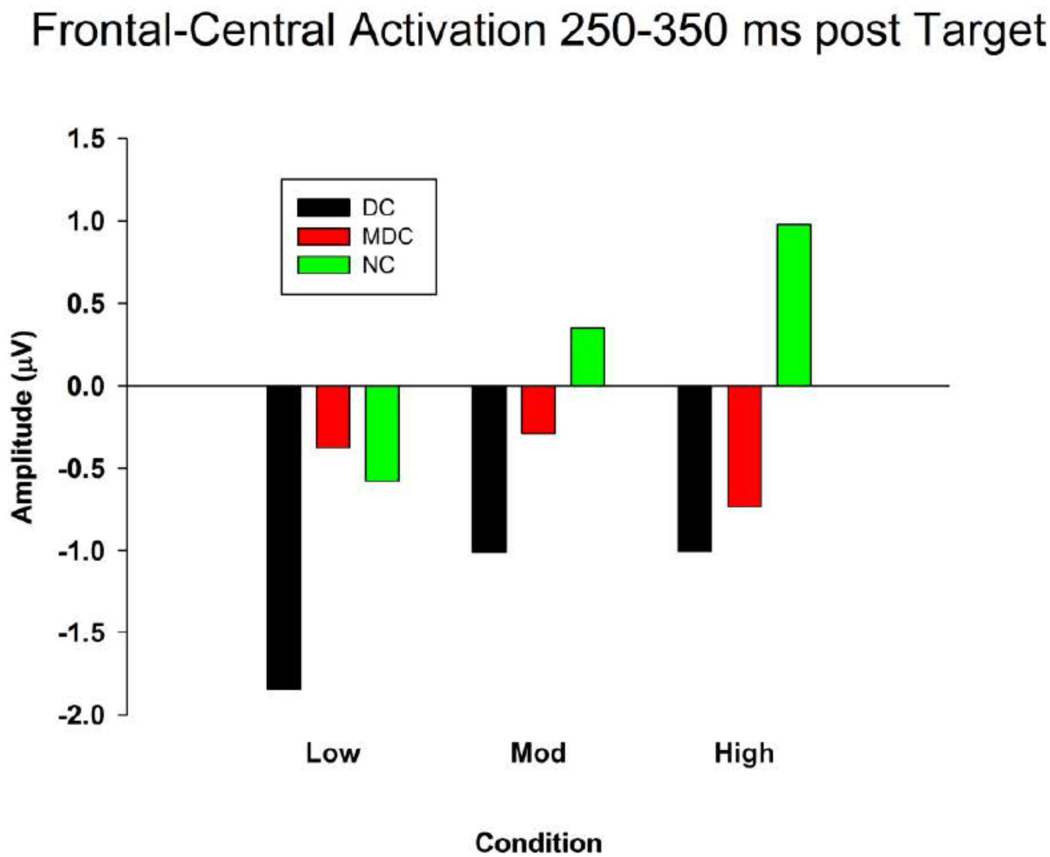
Graph 7


Fusion Coastal Drive: Average Swerving
Average SD of Distance from Center of Lane
.150
.125
.100
.075
.050
Low
Moderate
High
Cognitive Workload

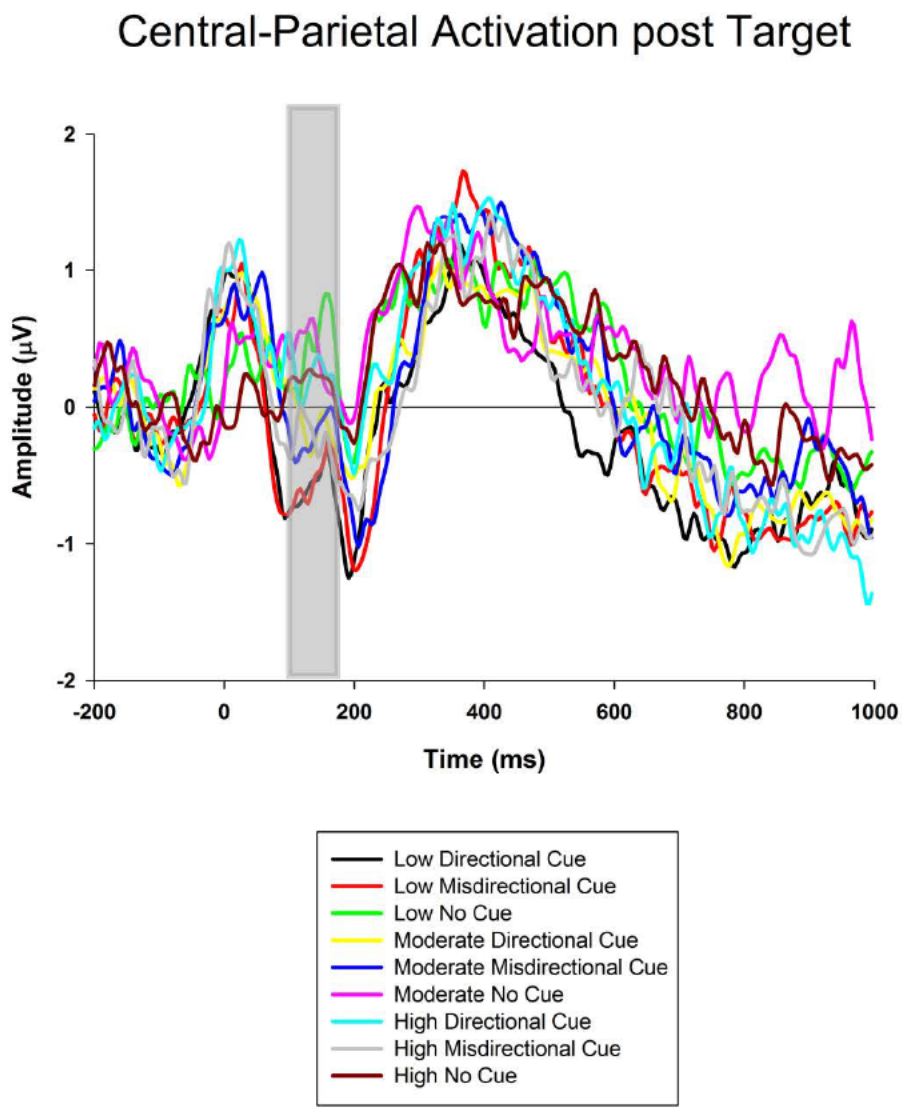
Graph 8


Frontal-Central Activation post Target
Amplitude (μV)
2
1
0
-1
-2
-3
-4
-200
0
200
400
600
800
1000
Time (ms)
Low Directional Cue
Low Misdirectional Cue
Low No Cue
Moderate Directional Cue
Moderate Misdirectional Cue
Moderate No Cue
High Directional Cue
High Misdirectional Cue
High No Cue

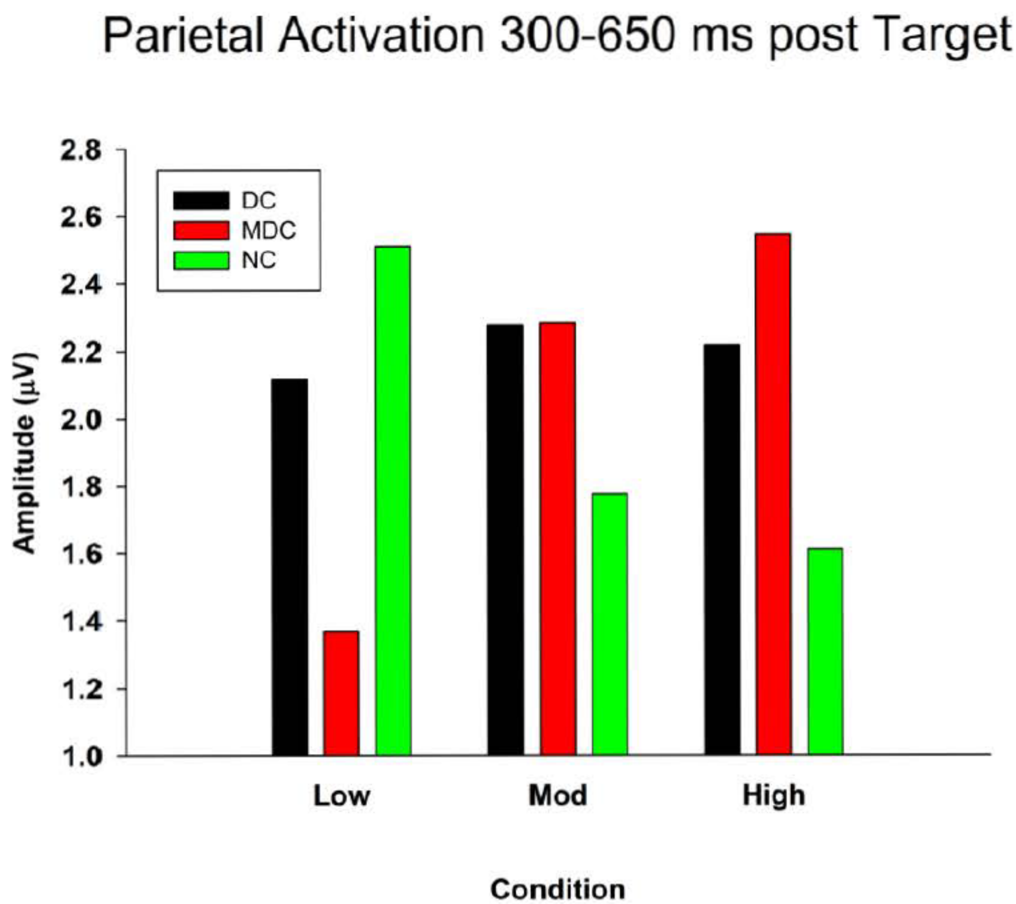
Graph 9


Frontal-Central Activation 250-350 ms post Target
DC
MDC
NC
Amplitude (µV)
1.5
1.0
0.5
0.0
-0.5
-1.0
-1.5
-2.0
Low
Mod
High
Condition

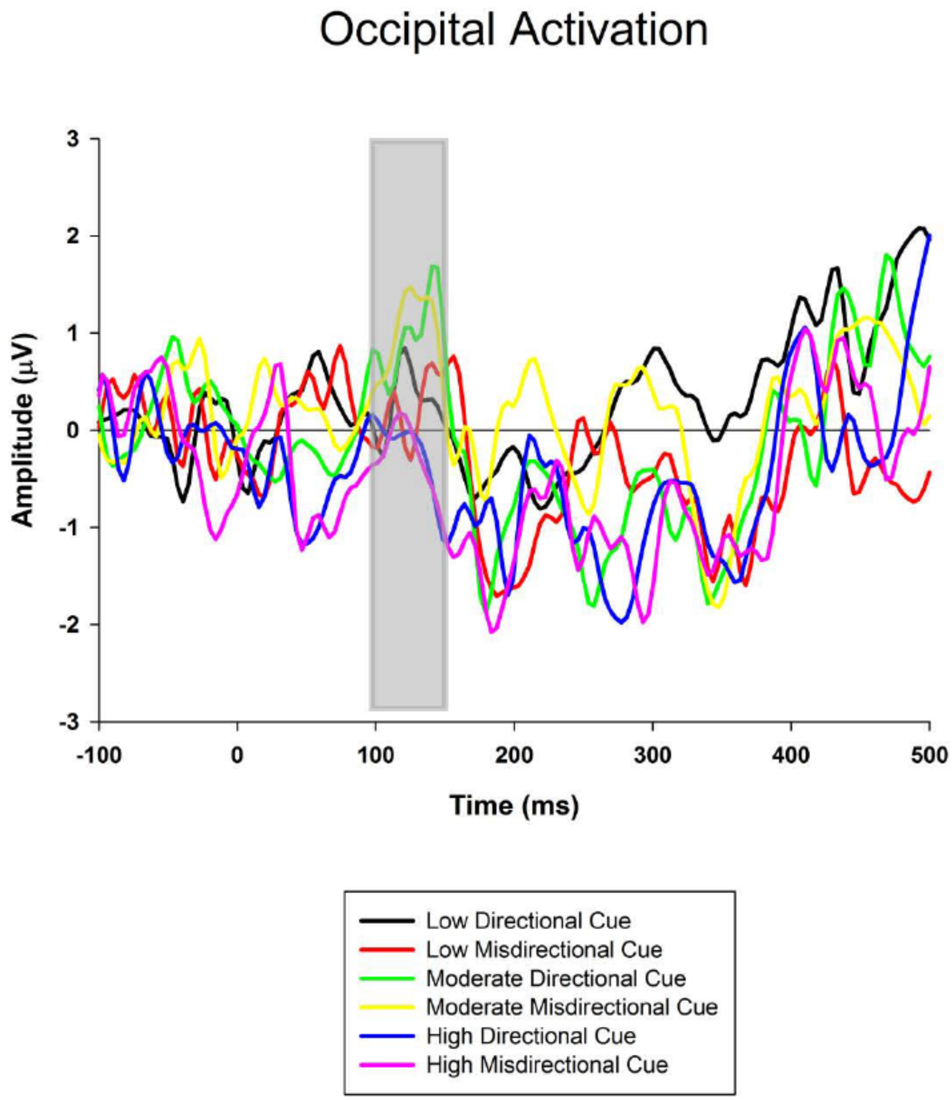
Graph 10


Central-Parietal Activation post Target
Amplitude (μV)
2
1
0
-1
-2
-200
0
200
400
600
800
1000
Time (ms)
Low Directional Cue
Low Misdirectional Cue
Low No Cue
Moderate Directional Cue
Moderate Misdirectional Cue
Moderate No Cue
High Directional Cue
High Misdirectional Cue
High No Cue

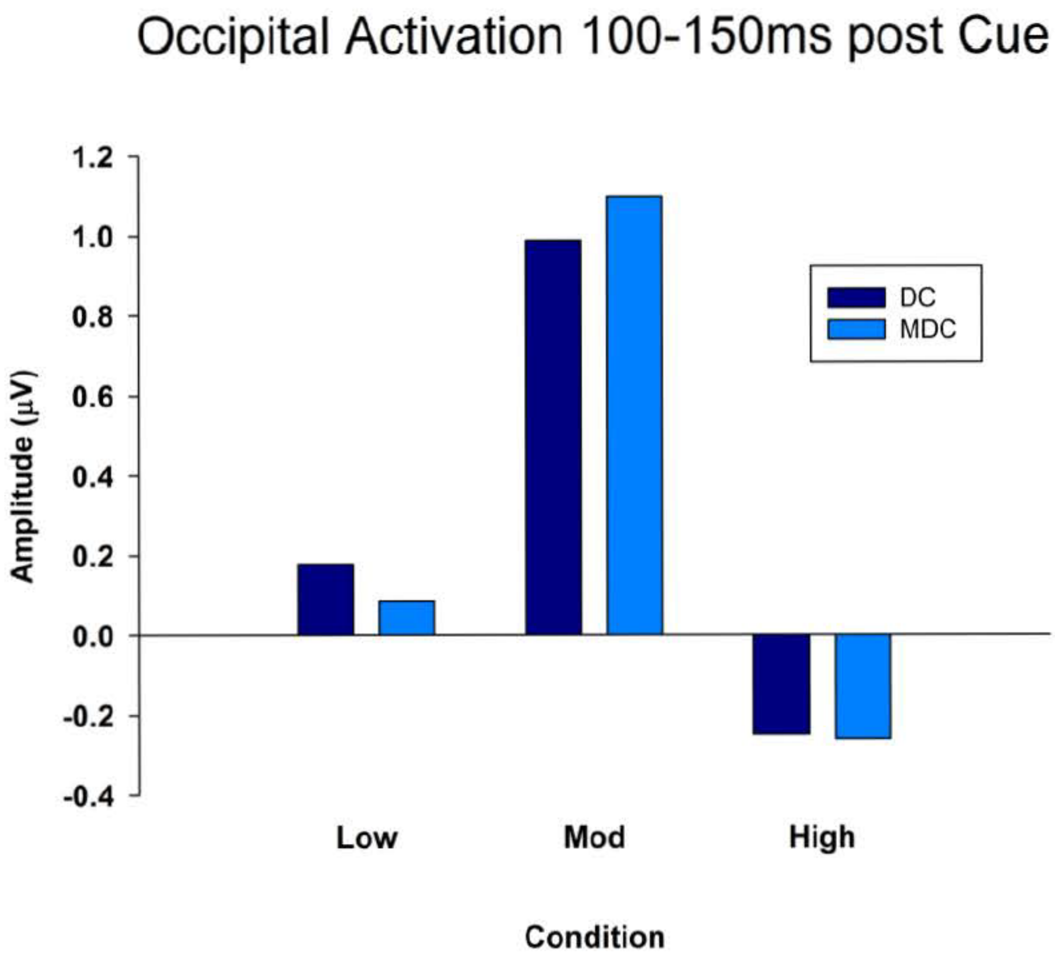
Graph 11


Parietal Activation 300-650 ms post Target
DC
MDC
NC
Amplitude (μV)
2.8
2.6
2.4
2.2
2.0
1.8
1.6
1.4
1.2
1.0
Low
Mod
High
Condition

Graph 12


Occipital Activation
3
2
1
0
-1
-2
-3
-100
0
100
200
300
400
500
Amplitude (μV)
Time (ms)
Low Directional Cue
Low Misdirectional Cue
Moderate Directional Cue
Moderate Misdirectional Cue
High Directional Cue
High Misdirectional Cue

Graph 13



Occipital Activation 100-150ms post Cue
1.2
1.0
0.8
0.6
0.4
0.2
0.0
-0.2
-0.4
Amplitude (µV)
DC
MDC
Low
Mod
High
Condition